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Cardiac Function in Smokers and Nonsmokers: The CARDIA Study

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Objectives. **This study assessed clinical and echocardiographic measures of cardiac function at rest in smokers and nonsmokers to determine the associations of cigarette smoking with various measures of left and right ventricular performance.**

Background. **Whereas the immediate cardiovascular effects of cigarette smoking have been well described, the long-term effects in an otherwise healthy cohort have not. Of particular interest were associations with heart rate, left ventricular end-systolic stress and left ventricular mass because higher levels of these measures would suggest increased myocardial oxygen consumption.**

Methods. **In year 5 of the Coronary Artery Risk Development in Young Adults (CARDIA) study, 3,366 smokers and nonsmokers (ex-smokers were excluded) underwent echocardiography as well as assessment of heart rate, anthropometric measurements and blood pressure. Participants ranged in age from 23 to 35 years and were equally distributed by race and gender. Echocardiographic measures included pulsed Doppler pulmonary artery acceleration time (a decrease suggests increased pulmonary artery pressure), left ventricular mass, left ventricular end-systolic stress and left ventricular fractional shortening.**

Results. **All comparisons were between smokers and nonsmokers. Heart rate at rest was significantly higher in smokers by 1.5 to 5 beats/min in all race/gender groups except black men. In men who smoked, pulmonary artery acceleration time was significantly lower by 4 to 8 ms. Except for black male smokers, there was a trend toward increased left ventricular mass (3 to 8 g) in all race/gender groups, significant in black women. Left ventricular end-systolic stress was significantly higher in women who smoked (4 to 6 dynes/cm^2). There were no differences for systolic blood pressure or left ventricular fractional shortening.**

Conclusion. **In an assessment of cardiovascular function at rest in young adults, quantifiable differences between smokers and nonsmokers that predict increased rest myocardial oxygen consumption in smokers were found. Some of these differences were gender specific.**

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Cigarette smoking is accompanied by a plethora of physiologic effects. Immediately after smoking a cigarette, heart rate, blood pressure and carboxyhemoglobin concentration increase; coronary arteries vasoconstrict; and exercise tolerance diminishes (1–4). Long-term physiologic effects, observed after an interval free from cigarettes, include a persistence of abnormal exercise tolerance, an increased tendency to thrombosis, diminished coronary artery flow reserve, increased hemoglobin concentration, decreased lung function and normal or slightly decreased blood pressure (5–9). The net consequence of these hemodynamic and physiologic changes is to decrease systemic oxygen transport and increase the likelihood of coronary ischemia.

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Studies of the long-term associations of cigarette smoking with rest cardiac function in generally healthy populations have been limited to measurement of blood pressure and heart rate. In the 1990 to 1991 examination of >4,000 black and white men and women in the Coronary Artery Risk Development in Young Adults (CARDIA) study (10), echocardiographic studies were performed, which allowed the testing of specific hypotheses concerning the cross-sectional relations between cigarette smoking and cardiac function at rest. Of particular interest were differences between smokers and nonsmokers with regard to heart rate, left ventricular systolic function and left ventricular end-systolic stress because increases in these measures would be associated with increased rest myocardial oxygen consumption (11). The influence of race and gender on these relations was also assessed.

Methods

Study population. The CARDIA cohort initially included 5,115 participants 18 to 30 years old in 1985 to 1986 and approximately equally divided by race, gender and educational level. Participants were recruited and examined at four field centers located in Chicago, Illinois; Birmingham, Alabama; Minneapolis, Minnesota; and Oakland, California. The purpose of the study was to describe the evolution of cardiovas-

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cular risk through young adulthood. Details of overall study design and participant recruitment have previously been described (12). Participants were recruited from the community and a large health plan to represent a generally healthy cross section of young adult Americans. Every attempt was made to obtain a representative cross section of the young adult population, and no individual was excluded because of smoking status.

Echocardiographic studies were performed at the third examination (1990 to 1991, year 5) in 4,243 of 4,352 returning participants. At this time, participants were 23 to 35 years old, and of these, 3,970 had M-mode echocardiographic studies of sufficiently good quality for analysis. Ex-smokers (n = 554) were excluded for simplicity of analysis. Also, subjects with heart disease, diagnosed by echocardiography of sufficient severity to confound analysis (e.g., significant valve regurgitation, cardiomyopathy, n = 41) and those with missing information about smoking status (n = 9) were excluded. This left a final cohort of 3,366.

Echocardiographic protocol. The study protocol has previously been described and was similar to that used in the Cardiovascular Health Study (10,13). In general, participants had not smoked for 2 to 8 h before the start of the study. Each participant underwent two-dimensional echocardiography, Doppler interrogation of the aortic and mitral valves, pulsed Doppler pulmonary artery flow recording and two-dimensionally guided M-mode echocardiography. All studies were performed on an Acuson cardiac ultrasound machine (Acuson, Inc.), recorded on videotape and read at a central reading center located at the University of California–Irvine.

Measurements used in this study were obtained from the two-dimensionally guided M-mode echocardiography of the left ventricle and the Doppler study of the proximal pulmonary artery. M-mode measurements were made according to recommendations of the American Society of Echocardiography (14). Left ventricular mass, left ventricular fractional shortening and left ventricular end-systolic stress were calculated according to standard formulas (15,16):

Left ventricular mass (g)

$$= 0.80 \times \{1.04[(VSTd + LVIDd + PWTd)^3 - (LVIDd)^3]\} + 0.6;$$

Left ventricular fractional shortening (%)

$$= (LVIDd - LVEDs)/LVIDd \times 100;$$

Left ventricular end-systolic stress (dynes/cm^2)

$$= 0.334P \times (LVIDs)/[1 + (PWTs/LVIDs)]PWTs,$$

where VSTd = ventricular septal thickness at end-diastole; LVIDd = left ventricular internal dimension at end-diastole; PWTd = posterior wall thickness at end-diastole; LVEDs = left ventricular end-systolic dimension; P = left arm cuff pressure; LVIDs = left ventricular internal dimension at end-systole; and PWTs = posterior wall thickness at end-systole.

Left ventricular mass was then divided by body surface area to index for body frame size. Other methods of indexing, including use of body mass index (kg/m^2) and using weight and height independently in multivariate models were also used; results were similar regardless of the method used. The pulmonary artery Doppler tracing was obtained with the Doppler sample volume placed just distal to the pulmonary valve and parallel to flow. An additional 220 participants were excluded from analyses of pulmonary artery Doppler flow because adequate studies for analysis were not obtained. Pulmonary artery acceleration time was measured as the time interval from the onset of flow across the pulmonary valve to the attainment of peak flow velocity (17). Pulmonary artery acceleration time has previously been shown (18) to be inversely related to pulmonary artery pressure and resistance, components of right ventricular afterload.

Technical errors for components of variability for left ventricular mass measurements were as follows: for intratechnician performance, 10% (from 60 paired studies); for intertechnician performance, 10% (from 44 paired studies); for intrareader, 8% (from 158 paired studies); and for interreader, 14% (from 350 paired studies) (13).

Clinical measures. Smoking status was assessed by questionnaire. Nonsmokers were those who had never smoked or who had smoked <5 cigarettes/day for <3 months. Ex-smokers were those who had previously smoked >5 cigarettes/day for at least 3 months but were not currently smoking. Current smokers were those who smoked >5 cigarettes/day and who had smoked for >3 months. Average number of cigarettes smoked per day was assessed for the current smokers. The three subjects who smoked pipes (all nonsmokers) or the seven who smoked cigars (five smokers, two nonsmokers) were evaluated on the basis of their cigarette-smoking habit. The average weekly consumption of alcohol was calculated from questionnaire information (19). Height was measured to the nearest 0.5 cm, and weight was measured to the nearest 0.2 lb while the participants were wearing light clothing and no shoes.

Systolic blood pressure, diastolic blood pressure and heart rate were measured after the participant had been seated quietly for 5 min. Blood pressure was measured three times using a random zero sphygmomanometer, with the average of the second and third readings used in this analysis. Heart rate was measured for 30 s, multiplied by 2, and expressed as beats/min. Forced expiratory flow volume in 1 s (FEV_1) was measured according to American Thoracic Society recommendations using a Collins Survey Spirometer and an Eagle II microprocessor (20). Physical activity was assessed using a questionnaire modified from the Minnesota leisure time activity score and was designed to measure moderate and intense physical activity (21).

Data analysis. Analyses were performed using the Statistical Analysis System software package (SAS System). Initial analyses were performed for subgroups defined by race, gender and smoking status. Descriptive statistics were calculated, and smokers were compared with nonsmokers using the Student *t* test. Analyses were repeated after adjustment for age, race,

Table 1. Selected Variables for the Cohort by Race and Gender (mean ± SD)

	Black Men		Black Women		White Men		White Women	
	Smokers (n = 305)	Nonsmokers (n = 443)	Smokers (n = 338)	Nonsmokers (n = 663)	Smokers (n = 227)	Nonsmokers (n = 562)	Smokers (n = 234)	Nonsmokers (n = 594)
No. of yr smoked regularly	10.8 ± 7.0		11.3 ± 7.8		12.6 ± 5.2		11.3 ± 5.0	
No. of cigarettes/day	10.9 ± 7.4		10.3 ± 6.6		18.6 ± 10.4		14.1 ± 8.9	
Alcohol consumption/ day (ml)	30.8 ± 40.3*	11.1 ± 22.7*	10.0 ± 16.6*	2.6 ± 6.5*	26.7 ± 58.1*	11.6 ± 16.3*	10.6 ± 16.2*	4.7 ± 8.5*
Weight (lb)	172.6 ± 32.6*	187.2 ± 40.2*	162.9 ± 44.7	166.1 ± 45.7	175.5 ± 29.4	177.6 ± 30.0	150.9 ± 33.2†	143.9 ± 31.4†
Height (cm)	176.6 ± 7.3	177.5 ± 6.8	163.9 ± 6.6	163.6 ± 7.0	177.9 ± 6.6	178.3 ± 7.1	165.1 ± 6.2	165.5 ± 6.4
Systolic blood pressure (mm Hg)	113.3 ± 11.9	113.8 ± 11.2	106.7 ± 13.4	106.7 ± 9.9	108.8 ± 11.1	110.0 ± 10.1	102.2 ± 10.2	101.9 ± 9.2
Diastolic blood pressure (mm Hg)	71.3 ± 10.8‡	73.3 ± 10.2‡	68.3 ± 12.3	69.2 ± 9.3	69.6 ± 9.1	70.7 ± 9.3	64.1 ± 9.2‡	65.8 ± 8.5‡
LV fractional shortening (%)	34.6 ± 6.2	34.6 ± 6.2	36.6 ± 6.6	36.5 ± 5.9	35.0 ± 6.2	35.7 ± 5.6	35.4 ± 5.5‡	36.3 ± 5.3‡
Maximal FEV_1	3.7 ± 0.6	3.7 ± 0.6	2.8 ± 0.5	2.8 ± 0.5	4.3 ± 0.6†	4.4 ± 0.7†	3.2 ± 0.5†	3.3 ± 0.5†

*$p < 0.0001$, †$p < 0.01$, ‡$p < 0.05$, smokers versus nonsmokers. FEV_1 = forced expiratory flow volume in 1 s; LV = left ventricular.

gender, systolic blood pressure, physical activity score, alcohol use, height and weight by analysis of covariance. These variables are known to be associated either with smoking or critical outcome measures in this cohort (13). Adjustment for systolic blood pressure was not performed for heart rate or left ventricular end-systolic stress because systolic blood pressure and heart rate are linked by baroreceptor function, and systolic blood pressure is used in the calculation of left ventricular end-systolic stress. The FEV_1 was added to the model for pulmonary artery acceleration time because of possible interactions between lung function and pulmonary resistance. Height and weight were not used in the adjustment for left ventricular mass/body surface area.

Results

Race/gender-specific comparisons of smokers with nonsmokers segregated by race and gender for years of smoking, cigarettes smoked per day, alcohol intake, weight, height, systolic blood pressure, diastolic blood pressure, left ventricular fractional shortening and FEV_1 are shown in Table 1. Smokers consumed significantly more alcohol per day than did nonsmokers. Black male smokers weighed less than nonsmokers. Unexpectedly, white women smokers weighed more than nonsmokers. Diastolic blood pressure was slightly lower in black men and white women smokers than in nonsmokers. Left ventricular fractional shortening was minimally decreased in white women who smoked. The FEV_1 was slightly lower in white smokers. No other comparisons between smokers and nonsmokers attained statistical significance.

Figure 1 shows comparisons between smokers and nonsmokers for key study end points by race and gender. Heart rate at rest was higher in smokers than nonsmokers for all race/gender groups except black men ($p < 0.01$ for black women; $p < 0.0001$ for whites). Pulmonary artery acceleration time, a measure of right ventricular afterload, was lower in male smokers ($p < 0.05$ for black men; $p < 0.01$ for white men). Left ventricular mass/body surface area was increased in black women who smoked ($p < 0.0001$). Left ventricular end-systolic stress, an index of left ventricular afterload, was higher in women who smoked ($p < 0.01$).

Results of comparisons made after adjustment for potential confounders (age, weight, height, physical activity, blood pressure, FEV_1 and alcohol use) are shown in Table 2. Left ventricular mass/body surface area showed a clear trend toward significantly higher mass (2 to 5 g/m^2) in smokers in all four race/gender groups. Heart rate remained significantly higher in smokers (1.5 to 5 beats/min) except for black men. Results for pulmonary artery acceleration time were unchanged. Left ventricular end-systolic stress was increased, or there was a trend toward an increase, in all race/gender groups except for white men.

Discussion

The present study showed that cardiac function at rest differs in smokers and nonsmokers. Smokers have a higher rest heart rate, lower pulmonary artery acceleration time, higher left ventricular mass and higher left ventricular end-systolic stress. Smokers did not differ from nonsmokers with regard to blood pressure or left ventricular systolic function as assessed by left ventricular fractional shortening. Thus, several major determinants of myocardial oxygen consumption were higher in smokers (10). The direction of difference is consistent with increased rest myocardial oxygen consumption. However, the magnitudes of these associations are small and would not be associated with any clinical symptoms in this cohort.

Physiologic effects of smoking. Several physiologic effects of cigarette smoking may help to explain the findings in this study. Studies of subjects while actively smoking have sug-

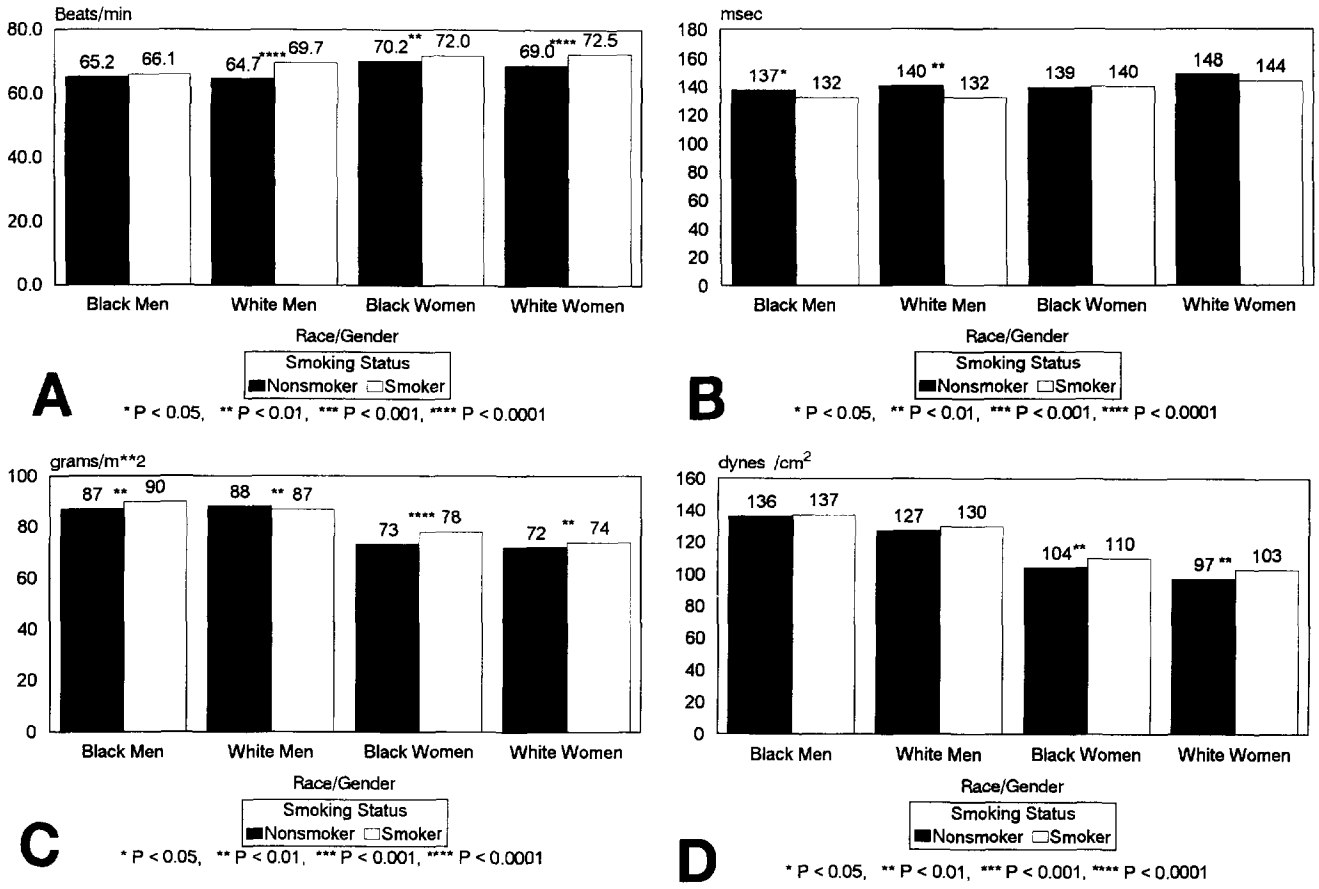

Figure 1. Unadjusted comparisons between smokers and nonsmokers by race and gender for **(A)** heart rate, **(B)** pulmonary artery acceleration time, **(C)** left ventricular mass/body surface area and **(D)** left ventricular end-systolic stress.

gested that autonomic regulation of heart rate variability may be different in smokers than in nonsmokers (22). An immediate decline in heart rate has been observed during smoking cessation attempts (23). This is followed by a slow increase in heart rate toward basal levels over several months. Also, smokers have diminished exercise tolerance; their increase in resting heart rate may be related to poorer physical fitness (6).

A decreased pulmonary acceleration time may be secondary to increased pulmonary vascular resistance (18). The difference observed in this study is small and does not reflect an elevation of resistance to pathologic levels. However, this increase in resistance may be secondary to mild hypertrophy of small pulmonary arterial vessels induced by the alveolar hypoxemia associated with smoking or from ventilation/perfusion inequalities in poorly ventilated alveoli (24).

Higher left ventricular mass and wall stress may be inter-

Table 2. Comparison Between Current Smokers and Nonsmokers for Selected Variables After Adjustment for Age, Height, Weight, Alcohol Consumption per Day, Physical Activities and Other Variables by Race and Gender

	Black Men		Black Women		White Men		White Women	
	Smokers (n = 305)	Nonsmokers (n = 443)	Smokers (n = 338)	Nonsmokers (n = 663)	Smokers (n = 227)	Nonsmokers (n = 562)	Smokers (n = 234)	Nonsmokers (n = 594)
Heart rate (beats/min)	65.9	65.5	72.1*	70.2*	69.4†	64.8†	72.2†	69.0†
Pulmonary artery acceleration time (ms)	132‡	136‡	141	138	132§	140§	146	148
LV mass/body surface area (kg/m^2)	90	88	78†	73†	87	85	74	72
LV wall stress (dynes/cm^2)	138	136	110§	104§	130	128	102‡	98‡

*$p < 0.01$, †$p < 0.0001$, ‡$p < 0.05$, §$p < 0.001$, smokers versus nonsmokers. See text for details of multivariate analyses. LV = left ventricular.

related. The left ventricle responds to increases in afterload by initially dilating and then by increasing mass to compensate for the increased wall stress caused by chamber dilation (25). Small immediate increases in blood pressure occur with each cigarette smoked (1,9). Significant peripheral vascular disease and changes in the regulation of peripheral vascular resistance are known to occur in smokers (26,27). Therefore, the higher left ventricular wall stress may reflect early changes in the peripheral vasculature. A recent study (28) of the effects of smoking on distensibility and compliance of the carotid and brachial arteries compared smokers immediately after smoking with nonsmokers. Immediate short-term increases in arterial wall stiffness were present in the smokers.

It is important to adjust left ventricular mass for a measure of body size in a study such as this because body size is the main determinant of left ventricular mass (13). In the present study, the relation between smoking and left ventricular mass was independent of body size. Indexing for body size helped clarify the relation to smoking because of the divergent relation between smoking status and weight in black men and white women. The finding that white women smokers weighed more than nonsmokers was unexpected; perhaps it related to the fact that the women smokers were less physically fit (6).

It is not clear why associations with pulmonary artery acceleration time were more pronounced in men, whereas associations with left ventricular afterload were more pronounced in women. White men had the highest reported number of cigarettes smoked per day and years of smoking, but this group did not show the most extreme effects for all variables. It could be speculated that the effects of smoking are greater in the pulmonary vascular bed of men, whereas they are greater in the systemic vascular bed of women. However, there are little data to support a biologic mechanism for this speculation. Complex interactions are present among cigarette smoking, exercise tolerance and physical fitness. Because there are significant race/gender differences in physical fitness, fitness may also have an effect on the race/gender differences observed (6,29). Nonetheless, gender-specific effects should be considered in future physiologic and pathologic studies of tobacco exposure.

Summary. Changes in cardiovascular function at rest consistent with increased rest myocardial oxygen consumption can be added to the list of chronic sustained physiologic effects of cigarette smoking. This list includes decreased exercise tolerance, diminished lung function, an increased tendency to thrombosis and abnormalities of vascular regulation in both the peripheral and coronary circulations (3,5–8,26–28). These changes have been demonstrated in a cohort with an average duration of smoking of 10 to 12 years. They are unlikely to be of sufficient magnitude to cause clinical symptoms but could be potential antecedents of cardiovascular morbidity later in life. For example, increased left ventricular mass has been shown to be an independent predictor of cardiac morbidity, and altered pulmonary acceleration time could reflect early chronic lung disease (30). The documented cardiovascular associations with cigarette smoking in relatively healthy young adults may represent subclinical disease and provide further delineation of the undesirable physiologic effects of smoking. Further studies are needed in an older cohort to further understand the importance of cigarette smoking to the evolution of cardiovascular disease, particularly with regard to the interaction of cardiac function with coronary artery disease outcomes.

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